Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort[1–3]

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ABSTRACT

Background: Dairy intake may increase prostate cancer risk, but whether this is due to calcium's suppression of circulating vitamin D remains unclear. Findings on calcium and vitamin D intake and prostate cancer are inconsistent.

Objective: We examined the association of dairy, calcium, and vitamin D intake with prostate cancer.

Design: In a prospective study of 3612 men followed from 1982–1984 to 1992 for the first National Health and Nutrition Examination Epidemiologic Follow-up Study, 131 prostate cancer cases were identified. Dietary intake was estimated from questionnaires completed in 1982–1984. Relative risk (RR) and 95% CIs were estimated by using Cox proportional hazards models adjusted for age, race, and other covariates.

Results: Compared with men in the lowest tertile for dairy food intake, men in the highest tertile had a relative risk (RR) of 2.2 (95% CI: 1.2, 3.9; trend $P = 0.05$). Low-fat milk was associated with increased risk (RR = 1.5; 95% CI: 1.1, 2.2; third compared with first tertile; trend $P = 0.02$), but whole milk was not (RR = 0.8; 95% CI: 0.5, 1.3; third compared with first tertile; trend $P = 0.35$). Dietary calcium was also strongly associated with increased risk (RR = 2.2; 95% CI: 1.4, 3.5; third compared with first tertile; trend $P = 0.001$). After adjustment for calcium intake, neither vitamin D nor phosphorus was clearly associated with risk.

Conclusions: Dairy consumption may increase prostate cancer risk through a calcium-related pathway. Calcium and low-fat milk have been promoted to reduce risk of osteoporosis and colon cancer. Therefore, the mechanisms by which dairy and calcium might increase prostate cancer risk should be clarified and confirmed. *Am J Clin Nutr* 2005;81:1147–54.

KEY WORDS Dairy, diet, calcium, vitamin D, prostatic neoplasms

INTRODUCTION

Both ecologic (1) and epidemiologic studies (2) have fairly consistently found an increase in prostate cancer risk with intake of dairy foods. A strong ecologic correlation between milk intake and prostate cancer mortality was noted as early as 1975 (1), and in a more recent ecologic analysis, the correlation was stronger for milk and prostate cancer mortality than for any other dietary factor, including red meat (3). Among epidemiologic studies, 7 of 10 prospective studies found a positive association between dairy intake and prostate cancer risk (2, 4). Studies that examined individual types of dairy products show more consistent findings for milk (2), probably because milk is the most commonly consumed form of dairy. Although initial explanations for the observed dairy effect related to the fat content in dairy foods, the hypothesis that 1,25-dihydroxyvitamin D (1,25-D) might protect against prostate cancer (5) suggests another possible mechanism: that at sufficiently high amounts, dietary calcium suppresses production of 1,25-D, thereby increasing risk of prostate cancer (6).

The observation that dairy may increase risk of prostate cancer is troubling, given current dietary recommendations for calcium intake (7), aggressive promoting of dairy as a source of calcium (8), and the possibility that calcium intake may protect against colon cancer (9). The objective of this analysis was to examine the associations of dairy food, calcium, and vitamin D intake with prostate cancer risk, to determine whether previous findings can be confirmed, and to assess the extent to which associations observed for dairy might be due to their calcium content, possibly through a vitamin D-related pathway.

SUBJECTS AND METHODS

Study population

The study sample included male participants in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS). NHANES I, conducted between 1971 and 1975, used a multistage sampling design to obtain a national probability sample of the noninstitutionalized civilian population of the United States, excluding Alaska, Hawaii, and Native American reservation lands (10, 11). The elderly and persons residing in poverty areas were oversampled. Of the persons selected ≈70% were both interviewed and medically examined in NHANES I.

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NHEFS was a longitudinal study of the 14 407 NHANES I participants between the ages of 25 and 74 y at the time of the initial survey (12–15). Participants were followed for health and vital status through 1992. At interviews conducted in 1982–1984, 1986, 1987, and 1992, participants or their proxies were interviewed. Also, health records were obtained for overnight stays in a health care facility occurring after the baseline examination. Through the National Death Index and other tracing mechanisms, death certificates were obtained for deaths during the follow-up period. Health records were obtained for >70% of overnight stays reported by subjects, and death certificates were obtained for 99% of deaths occurring between 1971–1975 and the 1992 follow-up (15). The procedures followed for NHEFS were in accordance with the ethical standards of the National Center for Health Statistics, which conducted the survey, and approval for the survey was obtained from the center's Ethical Review Board.

Because the 1982–1984 interview included more detailed questions on dietary habits and intake than the interview conducted in 1971–1975, the 1982–1984 interview served as the baseline for these analyses. Of the 14 407 NHEFS participants, 5811 were men. Of these, 1202 had died before the 1982–1984 interview, 351 could not be traced, and 333 were traced but not interviewed in 1982–1984. Subjects were also excluded if they had a diagnosis of prostate cancer at or before the 1982–1984 interview ($n = 57$), did not complete the diet questionnaire ($n = 79$), or reported an energy intake of <500 or >4400 kcal/d ($n = 10$), which left 3779 men available for analysis.

Identification of prostate cancer cases

Cases of invasive prostate cancer were identified, following a procedure described by Breslow et al (16). Briefly, potential cases were all men with an International Classification of Diseases, Ninth Revision, Clinical Modification code of 185 (invasive prostate cancer), 233.4 (prostate carcinoma in situ), v10.46 (personal history of malignant prostate neoplasm), or 60.3–60.5 (prostatectomy surgical procedures) recorded in at least one of the following ways: *1*) a first diagnosis of prostate cancer reported at any of the follow-up interviews conducted in 1986, 1987, or 1992; *2*) at least 1 hospital stay during the follow-up period with a discharge diagnosis coded as any of the above-mentioned codes; or *3*) a death certificate with underlying or nonunderlying cause of death coded as any of the above-mentioned codes. Archived records of interviews and overnight stays in a health care facility were then reviewed. None of the prostate cancer cases identified were in situ cases. "Definite" case status was assigned if a diagnosis of prostate cancer could be confirmed from histopathology reports or medical records, whereas determinations that were based only on interview or death certificate data were assigned "probable" case status. Of 136 cases diagnosed during follow-up of the 3779 men between 1982–1984 and 1992, 89 were considered definite cases, and 47 were considered probable cases.

Data collection

Information on dietary intake was obtained from a 105-item food-frequency questionnaire administered in the 1982–1984 interview. The questionnaire included 7 dairy items: whole or evaporated milk; low-fat, skim, dry, or butter milk; cheese or cheese dishes; yogurt; cream or sour cream; cottage cheese; and ice cream. Intake of specific nutrients such as energy, calcium, and phosphorus was estimated by multiplying frequency of intake of each food by the nutrient content for the food's portion size. Because the 1982–1984 NHEFS dietary interview collected only frequency information, information on nutrient content and portion size for each food item was based on sex- and age-specific 24-h recall data from the second National Health and Nutrition Examination Survey (NHANES II), a separate national survey conducted in 1976–1980. A detailed description of the method used to assign nutrient content and portion size to each food item in the NHEFS dietary questionnaire by using NHANES II data has been published (17).

We used the same procedures to assign sex- and age-specific vitamin D content per portion size to food items. International Units (IU) of vitamin D per 100 g food were based on the current US Department of Agriculture (USDA) nutrient database (18), supplemented with other published values (19). USDA values for vitamin D are based primarily on published data from 1991 (20), with some values updated for ready-to-eat cereals (18). Food intake for our study sample was assessed in 1982–1984, but, with the exception of ready-to-eat cereals, vitamin D values are unlikely to have changed substantially for the principal sources between 1982–1984 and 1991: vitamin D in seafood occurs naturally, and the recommendation that fortified milk contains 400 IU/qt has been in place since 1957 (21).

To estimate the amount of vitamin D in foods with vitamin D–containing ingredients such as cheese dishes or milk-containing baked goods, we used recipes available from the USDA Survey Nutrient Database for the 1994–1996 Continuing Survey of Food Intakes by Individuals (22) and other recipe sources (23, 24). Because dairy products used as ingredients in commercial items may not all be vitamin D–fortified (The National Dairy Council, personal communication, 2002), we assumed that milks and cheeses in commercially made items were not fortified, and that vitamin D–fortified milks and cheeses were used only in mixed dishes specified as homemade, from a home recipe, or from a mix. Among 56 milk- or cheese-containing commercial food items for which recipes were obtained, the average difference between the commercial items and their homemade counterparts was 10 IU vitamin D/100 g food.

Participants were also asked about their current use in 1982–84 of multivitamins and of any other vitamins, minerals, or nutritional supplements. Supplements were identified as calcium supplements if the name included calcium, bone meal, oyster shell, or dolomite. Regular use of the antacid Tums was also considered use of a calcium supplement. Other information available from the 1982–84 interview included race, current place of residence, longest held occupation, current family income, first-degree family history of prostate cancer, current weight, current alcohol intake, current smoking behavior, current sun exposure, and current level of physical activity. Information on height and level of education was available from the 1971–1975 interview.

Data analysis

Follow-up time was calculated by subtracting the 1982–1984 interview date from date of last interview for noncases or from date of prostate cancer diagnosis for cases. For 4 cases identified from death certificate data only, the 1982–1984 interview date was subtracted from date of death rather than from date of diagnosis.

We used Cox proportional hazards models adjusting for age (continuous years), race (white, black, or other race), and energy intake (tertiles) to estimate relative risk (RR) of prostate cancer for dairy foods and nutrients. Intake of dairy was calculated as the total intake of all 7 dairy food items in the questionnaire. Nutrient values, estimated from dietary sources only, were log-transformed as necessary and energy-adjusted by using the residual method (25). RRs were estimated for tertiles of intake relative to the lowest tertile, but, for infrequently consumed items such as yogurt and cream, estimates were for consumption compared with nonconsumption.

Other variables, including US region (Northeast, Midwest, South, West), residence (rural, urban, suburban), education (<high school, high school completion, >high school), first-degree family history of prostate cancer, current body mass index, recreational physical activity (little or none, moderate, much), usual level of daily activity (inactive, moderately active, very active), recreational (little, occasional, frequent) and occupational sun exposure, multivitamin use, smoking status (never, former, current), and past and current alcohol consumption (none, little, moderate, heavy), were evaluated as confounders on the basis of their associations with predictor and response variables and by comparing unadjusted and adjusted estimates from regression analyses. Final multivariate models included 3612 men with complete covariate data and adjusted for age; race; energy intake; US region; rural, urban, or suburban residence; education; recreational sun exposure; recreational and usual level of physical activity; smoking status; and current alcohol intake.

P values for trend were obtained for dairy food and nutrient intake by including an ordinal variable that included the median values for each category in the multivariate model controlling for the covariates listed in the preceding paragraph. To examine interactions between variables, we ran proportional hazards models with individuals cross-classified according to the variables of interest, which we dichotomized by grouping together tertiles with similar RR estimates (calcium tertile 3 compared with tertiles 1 + 2; vitamin D tertiles 2 + 3 compared with tertile 1). Although a post hoc decision, dichotomizing the variables in this way assumed that individuals in exposure categories similarly related to prostate cancer risk would show similar effects in relation to a potentially interacting variable and served to limit the number of categories to be compared.

Because of the possibility of inaccurate statistical adjustment in the tertile analysis because of high correlation between calcium and vitamin D intake, we also modeled energy-adjusted calcium and vitamin D as continuous predictors of prostate cancer. Although vitamin D was found to have a linear relation, we used a four-knot restricted cubic regression spline to model a nonlinear relation of calcium intake with risk (26).

Final models were run by using SUDAAN (27) to account for the stratification and cluster sampling of the NHANES I sample design. Unweighted analyses were conducted, but to account for the sample weighting in NHANES I we included the following design variables (variables that determine the sample weighting) (28) as covariates in the analyses: age (<65 compared with ≥65 y), poverty census enumeration district (residence compared with nonresidence), and family income (<$3000, $3000–$6999, $7000–$9999, $10 000–$14 999, and ≥$15 000), although estimates were similar in models without design variables.

TABLE 1
Descriptive characteristics and intake of selected foods and nutrients for 3612 adult male participants in the National Health Examination Follow-up Study at baseline, 1982–1984

Age (y)	57.8 ± 14.6[1]
Race [*n* (%)]	
White	3182 (88)
Black	384 (11)
Other	46 (1)
Region [*n* (%)]	
Northeast	1009 (28)
Midwest	969 (27)
South	747 (21)
West	887 (25)
Food intake (servings/wk)	
Dairy foods	12.9 ± 9.6
Total milk (low-fat + whole)	7.4 ± 7.7
Low-fat milk	3.8 ± 6.1
Whole milk	3.6 ± 6.1
Cheese	2.3 ± 2.6
Ice cream	1.8 ± 2.3
Cottage cheese	0.7 ± 1.5
Cream	0.5 ± 1.9
Yogurt	0.2 ± 1.1
Nutrient intake	
Energy (kcal/d)	1938 ± 610
Calcium (mg/d)	730 ± 347
Phosphorus (mg/d)	1317 ± 462
Vitamin D (IU/d)	172 ± 101

[1] $\bar{x}$ ± SD (all such values).

RESULTS

Descriptive characteristics of the study sample with complete covariate data are shown in **Table 1**. Mean age of the men was 57.8 y, 11% were African American, and their usual residence was roughly equally distributed among the 4 regions of the United States. The men consumed dairy foods almost twice a day on average. The most commonly consumed dairy items were low-fat and whole milk, cheese, and ice cream, whereas cottage cheese, cream, and yogurt were generally eaten less than once a week.

Over a mean follow-up of 7.7 y (range: <1–10.7 y), 131 prostate cancer cases were identified in the cohort of 3612 men. In Cox proportional hazards models (**Table 2**), dairy food intake (third compared with first tertile RR = 2.2; 95% CI: 1.2, 3.9; trend $P = 0.05$) was strongly associated with prostate cancer risk. When each dairy food was examined individually, the increase in risk was observed for total milk intake (third compared with first tertile RR = 1.8; 95% CI: 1.1, 2.9; trend $P = 0.03$) but for low-fat milk (third compared with first tertile RR = 1.5; 95% CI: 1.1, 2.2; trend $P = 0.02$) in particular. No elevation was observed for whole milk (third compared with first tertile RR = 0.8; 95% CI: 0.5, 1.3; trend $P = 0.35$) or for any other dairy food item. Because of a modest inverse correlation between low-fat milk and whole milk consumption (Pearson $r = -0.20$), we ran models that included both variables to account for possible confounding but saw no meaningful change in estimates.

Dietary calcium was also strongly associated with risk (third compared with first tertile RR = 2.2; 95% CI: 1.4, 3.5; trend $P = 0.001$) (**Table 3**). In addition, when we looked at calcium from different food sources, only calcium from low-fat milk was

TABLE 2
Adjusted relative risk (RR) estimates and 95% CIs for prostate cancer by tertile of dairy food intake for 3612 adult male participants in the National Health Examination Follow-up Study followed from 1982–1984 to 1992

	Median intake	Cases	Person-years	Minimal model RR (95% CI)[1]	Full model RR (95% CI)[2]
Dairy	*servings/wk*	*n*			
Tertile 1	5	32	9402	1.0	1.0
Tertile 2	11	38	9642	1.2 (0.7, 2.0)	1.1 (0.7, 1.9)
Tertile 3	21	61	8770	2.3 (1.3, 4.2)	2.2 (1.2, 3.9)
P for trend[3]				0.003	0.05
Total milk					
Tertile 1	0.5	34	9894	1.0	1.0
Tertile 2	7	47	10 415	1.2 (0.7, 2.0)	1.1 (0.7, 1.8)
Tertile 3	14	50	7505	1.9 (1.2, 3.2)	1.8 (1.1, 2.9)
P for trend				0.01	0.03
Low-fat milk					
Tertile 1	0	58	13 220	1.0	1.0
Tertile 2	1	15	5349	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)
Tertile 3	7	58	9245	1.6 (1.2, 2.2)	1.5 (1.1, 2.2)
P for trend				0.002	0.02
Whole milk					
Tertile 1	0	69	13 092	1.0	1.0
Tertile 2	1	21	5849	0.9 (0.5, 1.5)	0.9 (0.5, 1.7)
Tertile 3	7	41	8873	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)
P for trend				0.30	0.35
Cheese					
Tertile 1	0.25	44	7345	1.0	1.0
Tertile 2	1	50	11 867	1.0 (0.6, 1.5)	1.0 (0.7, 1.5)
Tertile 3	4	37	8602	1.1 (0.6, 1.9)	1.1 (0.6, 1.9)
P for trend				0.70	0.76
Ice cream					
Tertile 1	0.1	42	8638	1.0	1.0
Tertile 2	1.0	33	8851	0.9 (0.6, 1.5)	0.9 (0.6, 1.5)
Tertile 3	3.0	56	10 325	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)
P for trend				0.86	0.96
Cottage cheese					
Tertile 1	0	54	10 993	1.0	1.0
Tertile 2	0.3	19	6744	0.7 (0.4, 1.1)	0.6 (0.4, 1.1)
Tertile 3	1	58	10 077	1.3 (0.9, 1.8)	1.2 (0.8, 1.8)
P for trend				0.10	0.11
Cream					
no	0	101	18 775	1.0	1.0
yes	0.5	30	9039	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)
Yogurt					
no	0	113	23 023	1.0	1.0
yes	0.25	18	4791	1.1 (0.6, 1.9)	1.0 (0.6, 1.9)

[1] Adjusted for age, race, energy intake, and design variables.
[2] Additionally adjusted for US region; rural, urban, or suburban residence; education; recreational sun exposure; recreational and usual level of physical activity; smoking status; and current alcohol intake.
[3] Obtained by including in the model a variable representing the median value for each tertile.

clearly associated with risk (third compared with first tertile RR = 1.7; 95% CI: 1.1, 2.6; trend $P = 0.02$), although the association was not as strong as that for total calcium. Calcium from all other dietary sources, including calcium from whole milk, from all other dairy besides milk, and from nondairy sources, was not positively associated with risk (Table 3). We saw no elevation in risk for the 151 men (4%) who reported use of calcium supplements (RR = 0.9; 95% CI: 0.4, 2.3) or for the 846 men (23%) who reported use of multivitamins (RR = 0.9; 95% CI: 0.6, 1.5). Risk was also not especially elevated among 312 men in the highest tertile of calcium intake who were also users of multivitamins or calcium supplements relative to 1067 nonusers in the lowest tertile of calcium intake (RR = 1.9; 95% CI: 0.9, 3.7).

Phosphorus was not associated with risk of prostate cancer when calcium was also considered (third compared with first tertile RR = 0.9; 95% CI: 0.5, 1.6; trend $P = 0.77$), nor did we see evidence for any interaction between phosphorus and calcium intake. In contrast, with adjustment for calcium intake, vitamin D was inversely, although not significantly, associated with prostate cancer risk (third compared with first tertile RR = 0.6; 95% CI: 0.3, 1.2; trend $P = 0.16$; Table 3). Risk did not decrease, however, with intake of the principal food sources of vitamin D, namely low-fat or whole milk, fish, or shellfish, even

TABLE 3
Adjusted relative risk (RR) estimates and 95% CIs for prostate cancer by tertile of calcium, phosphorus, and vitamin D intake for 3612 adult male participants in the National Health Examination Follow-up Study followed from 1982–1984 to 1992

	Median intake[1]	Cases	Person-years	Minimal model RR (95% CI)[2]	Full model RR (95% CI)[3]	Full model + calcium RR (95% CI)
	mg/d or *IU/d*	*n*				
Calcium						
Tertile 1	455.4	28	9418	1.0	1.0	—
Tertile 2	642.1	37	9268	1.1 (0.7, 1.8)	1.0 (0.6, 1.7)	
Tertile 3	920.6	66	9128	2.4 (1.5, 3.9)	2.2 (1.4, 3.5)	
P for trend[4]				<0.001	0.001	
Calcium from low-fat milk						—
Tertile 1	0	31	9294	1.0	1.0	
Tertile 2	8.5	43	9232	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	
Tertile 3	264.9	57	9288	1.8 (1.2, 2.6)	1.7 (1.1, 2.6)	
P for trend				0.004	0.02	
Calcium from whole milk						—
Tertile 1	0	45	9463	1.0	1.0	
Tertile 2	6.9	40	9331	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)	
Tertile 3	193.8	46	9020	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)	
P for trend				0.21	0.27	
Calcium from all other dairy[5]						—
Tertile 1	50.1	43	9291	1.0	1.0	
Tertile 2	163.9	40	9487	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	
Tertile 3	337.8	48	9036	1.0 (0.6, 1.5)	0.9 (0.6, 1.5)	
P for trend				0.87	0.78	
Calcium from nondairy sources						—
Tertile 1	264.9	36	9430	1.0	1.0	
Tertile 2	330.1	45	9238	0.9 (0.6, 1.5)	0.9 (0.6, 1.4)	
Tertile 3	417.9	50	9146	0.9 (0.6, 1.4)	0.8 (0.5, 1.3)	
P for trend				0.61	0.42	
Phosphorus						
Tertile 1	984.0	39	9228	1.0	1.0	1.0
Tertile 2	1218.9	36	9269	1.0 (0.6, 1.4)	0.9 (0.6, 1.4)	0.7 (0.5, 1.1)
Tertile 3	1443.3	56	9317	1.6 (1.0, 2.5)	1.5 (1.0, 2.4)	0.9 (0.5, 1.6)
P for trend				0.04	0.08	0.77
Vitamin D						
Tertile 1	88	34	9391	1.0	1.0	1.0
Tertile 2	149	41	9205	0.9 (0.7, 1.4)	0.9 (0.6, 1.3)	0.7 (0.4, 1.1)
Tertile 3	239	56	9218	1.4 (0.9, 2.1)	1.3 (0.8, 2.1)	0.6 (0.3, 1.2)
P for trend				0.13	0.24	0.16

[1] mg/d for calcium and phosphorus; IU/d for vitamin D.
[2] Adjusted for age, race, energy intake, and design variables.
[3] Additionally adjusted for US region; rural, urban, or suburban residence; education; recreational sun exposure; recreational and usual level of physical activity; smoking status; and current alcohol intake.
[4] Obtained by including in the model a variable representing the median value for each tertile.
[5] Includes cheese or cheese dishes, yogurt, cream or sour cream, cottage cheese, and ice cream.

with adjustment for calcium intake. Because of concern about inaccurate risk estimates because of the substantial correlation (Pearson $r = 0.79$) between calcium and vitamin D intake, we computed additional models that included both as continuous variables and used a four-knot spline to model a nonlinear relation of calcium intake with prostate cancer risk. In these analyses, vitamin D was no longer associated with risk, but the strong positive association for calcium persisted (results not shown). Current use of cod liver oil was also not associated with prostate cancer risk (RR = 1.0; 95% CI: 0.2, 4.5), but only a small number of men ($n = 50$) reported its use. We found no evidence of effect modification when we examined relative risks for individuals cross-classified according to both calcium and vitamin D intake (P for interaction = 0.59).

In models for dairy foods that were additionally adjusted for calcium intake, associations for overall dairy (third compared with first tertile RR = 1.4; 95% CI: 0.6, 3.4; trend $P = 0.35$), total milk (third compared with first tertile RR = 0.9; 95% CI: 0.4, 1.9; trend $P = 0.78$), and low-fat milk (third compared with first tertile RR = 1.1; 95% CI: 0.7, 1.7; trend $P = 0.79$) were attenuated, whereas RR estimates and the trend P value for calcium were not meaningfully changed (data not shown).

Because low-fat milk consumption was associated with higher socioeconomic status, we explored the possibility that our findings for low-fat milk might be due to detection bias by controlling for potential surrogates of screening awareness or access, namely, level of education; poverty; and urban, rural, or suburban residence. Additional adjustment for these factors did not meaningfully change

the elevated risks observed for dairy, calcium, low-fat milk, or calcium from low-fat milk. Because of more widespread use of prostate-specific antigen (PSA) testing for prostate cancer screening after 1991, cases diagnosed from 1991 on probably included more early, slow-growing tumors, whereas cases diagnosed before 1991 were more aggressive. When we conducted analyses that included only 107 cases identified before 1991, the associations for low-fat milk (third compared with first tertile RR = 1.4; 95% CI: 1.0, 2.1; trend $P = 0.06$), calcium (third compared with first tertile RR = 2.0; 95% CI: 1.2, 3.4; trend $P = 0.007$), and calcium from low-fat milk (third compared with first tertile RR = 1.6; 95% CI: 1.0, 2.7; trend $P = 0.05$) were not meaningfully altered. Risk estimates were also not materially different when we limited cases more conservatively to the 46 identified before approval by the US Food and Drug Administration of PSA testing in 1986, excluded 14 prostate cancer cases diagnosed within a year of the dietary interview, reclassified 47 probable cases as noncases, or used age rather than time on study as the time scale (29).

Variables reflecting sun exposure that may also determine circulating vitamin D concentrations, including recreational and occupational sun exposure, reaction of the skin to sun exposure, ability to tan, and current residence in the southern region of the United States, were not associated with prostate cancer risk (results not shown). In a separate analysis (30), we saw evidence for an inverse association for intake of a southern pattern of food intake, characterized by such foods as cornbread, grits, sweet potatoes, and okra, possibly a marker of substantial cumulative sunlight exposure through longtime residence in the South (31). However, the southern dietary pattern did not significantly modify the effects of dairy, calcium, or vitamin D in these data. In race-specific analyses, associations of prostate cancer risk with dairy, calcium, and vitamin D intake were also similar.

DISCUSSION

Our findings are consistent with most studies that observed an elevated risk of prostate cancer with greater dairy or milk intake (2) and with several (4, 32–35) but not all (36–42) studies that observed an elevated risk with greater calcium intake. Our risk estimates for dairy and calcium are higher than some previously reported estimates (4, 32, 33) but comparable to those from the Health Professionals Follow-Up Study (34) and from a case-control study in King County, WA (35). In the Health Professionals cohort (34), RR estimates for advanced prostate cancer were 1.6 for >2 compared with 0 glasses milk/d, and 1.6 for ≥1000 compared with <600 mg Ca from food/d. In the King County, WA, study (35), odds ratio estimates for regional or distant disease were 2.1 for ≥2 compared with <2 glasses milk/wk, and 1.6 for ≥ 838 compared with <564 mg Ca from food/d. Effect estimates for calcium from food were more pronounced than for supplemental calcium in 2 (4, 35) of 3 (4, 34, 35) studies.

Notably, several previous studies that included larger proportions of cases diagnosed after the widespread adoption of PSA for screening saw stronger associations with calcium for more advanced disease than for the early, preclinical disease often detected by PSA screening (4, 34, 35). A distinct advantage of the current study is that most of the cases were diagnosed before more widespread PSA screening began in 1991 (43). Cases were, thus, less likely to be diagnosed incidentally and more likely to be advanced and clinically apparent, which allowed for a clearer examination of dairy and calcium intake in relation to clinically relevant disease.

Dairy foods may increase prostate cancer risk by raising circulating concentrations of insulin-like growth factor I (44, 45), but such a mechanism would not explain why we observed an association for low-fat milk only. Alternatively, calcium in dairy may increase risk by suppressing concentrations of circulating 1,25-D (6). Possibly, this mechanism is more applicable to low-fat milk than to other calcium sources. In the United States, milk is likely the most important source of bioavailable calcium because of its frequency of consumption and the ready absorption of calcium, especially in the presence of vitamin D added in fortification. Whereas the suppressive effects of calcium from whole milk may be countered by high intake of vitamin D, a similar reversal of calcium's effects may not occur with low-fat milk because fat-reduced milk products tend to have a lower vitamin D content (21, 46). Vitamin D, a fat-soluble vitamin, may also be less well absorbed from fat-reduced milk. Although a recent study found similar levels of absorption of vitamin D added to skim and whole milk (47), the quantity used in the study was 25 000 IU in 240 mL milk, substantially above the recommended amount of fortification in the United States of 400 IU/qt (7).

In fact, we found risk was elevated only for low-fat milk and not for whole milk or any other dairy food. When we examined calcium from different food sources, we saw no association for calcium from any source other than low-fat milk. We also saw no association for calcium supplements, although we were able to identify only 151 men who reported such use. In the Physicians' Health Study (33) as well, the elevated risk of prostate cancer associated with dairy and calcium intake was attributable primarily to intake of skim milk, and calcium intake from skim milk showed a stronger inverse correlation with plasma 1,25-D concentrations than did total dairy calcium. Although low-fat milk consumption may be recalled with less error than the consumption of other dairy products, it is unlikely that reporting would be so different between low-fat and whole milk, for example, as to result in complete attenuation of the association for whole milk. Our findings suggest, therefore, an effect attributable primarily to the consumption of low-fat milk, but whether because of its calcium content and vitamin D availability or to another characteristic of low-fat milk is not known. Removal of fat from milk, for example, may remove other components with potentially cancer-protective properties, such as conjugated linoleic acid (48).

Because men of higher socioeconomic status were more likely to drink low-fat milk, detection bias is another possibility. Since 1986, when the US Food and Drug Administration approved the PSA test for monitoring prostate cancer progression and prostate cancer screening, incidence has increased more steeply in men of higher socioeconomic status, who have better awareness of or access to screening modalities (49). Because PSA testing was relatively uncommon before 1991 (43), cases in our sample were more likely to be advanced cases. RR estimates were also largely unchanged when we limited cases to the 107 diagnosed before 1991, when we more conservatively limited cases to the 46 identified before government approval of PSA testing in 1986, and when we controlled for sociodemographic factors that might be linked to screening such as education (49).

Some previous studies suggest a protective effect for phosphorus with adjustment for calcium (32, 34). Phosphorous is found in a variety of food sources, although the principal contributors are milk, meat, poultry, and fish (50). Phosphorus has

been hypothesized to reduce risk by increasing parathyroid hormone concentrations or reducing calcium bioavailability in the intestine, resulting in higher 1,25D concentrations (32). We saw no effect for phosphorus or evidence of an interaction between calcium and phosphorus.

Although vitamin D is the central factor in the hypothesized mechanism that links calcium to prostate cancer risk, previous studies have not shown a protective effect for dietary vitamin D (32, 34, 35, 41). Some evidence links higher calcium intake with lower concentrations of circulating 1,25-D (33, 41); other studies (51, 52) have noted a protective effect of fatty fish, a principal source of vitamin D. In our cohort, we observed a suggestive protective effect for vitamin D when we combined vitamin D from all dietary sources, analyzed in tertiles, and adjusted for calcium intake. In additional analyses to reduce the potential for inaccurate estimates because of the high collinearity between calcium and vitamin D intake (53), however, vitamin D was no longer associated with risk, whereas the strong, positive association for calcium persisted. Further, even with adjustment for calcium intake, we observed no inverse association with risk of any single food or food group rich in vitamin D, including fish and seafood. Several factors contribute to the difficulty inherent in evaluating the effect of vitamin D effect on risk, including potential error in estimating vitamin D intake (7), the high collinearity between calcium and vitamin D intake, and the importance of both sunlight and diet in determining circulating vitamin D concentrations.

Sunlight has been hypothesized to protect against prostate cancer through 1,25-D production (5). A more recent work also offers evidence that childhood and cumulative, lifetime sun exposure is associated with reduced risk (54). Of the variables related to sunlight exposure that we examined, only adherence to a southern dietary pattern as an adult, possibly reflecting extended exposure to sunlight through longtime residence in the South, was inversely associated with prostate cancer risk (30). We found no evidence, however, that it significantly modified the effects of dairy, calcium, or vitamin D intake on prostate cancer risk.

A primary limitation of the study is that the diet questionnaire used in the 1982–1984 interview was not validated for estimating nutrient intake. Our estimates of calcium and phosphorus intake, however, are similar to independently derived 24-h recall estimates from the USDA 1994 Continuing Survey of Food Intakes by Individuals ($\bar{x}$ calcium: 750 mg/d; $\bar{x}$ phosphorus: 1307 mg/d for men aged 51–70 y) (7), and our estimate of vitamin D intake is only slightly higher than an independent estimate, based on 24-h recall data, of 143–148 IU/d for women participating in the 1971–1975 baseline survey of the NHEFS (55). Moreover, with little evidence of systematic bias in estimates, measurement error should generally attenuate associations.

An additional limitation is that, because typical supplement dosage could not be readily estimated from available data, we only considered dietary sources in estimating calcium and vitamin D intake. The small number of men who reported taking calcium ($n = 151$) or fish oil ($n = 50$) supplements further limited our ability to evaluate the effect of nondietary sources of these nutrients on disease risk. Finally, our findings were based on only a relatively small number of cases.

As discussed above, an important strength of the study is that, with a follow-up that ended in 1992, cases were less likely to be diagnosed incidentally through PSA testing and more likely to be clinically apparent and advanced, thus allowing for a clearer examination of dietary intake in relation to clinically relevant disease. Other strengths of the NHEFS include its prospective design; relatively long follow-up; excellent ascertainment of cancer outcomes; ethnically, socioeconomically, and geographically diverse population; and detailed diet questionnaire.

In summary, we found that prostate cancer risk was significantly elevated with higher intake of dairy foods and calcium, particularly calcium from low-fat milk. Our findings suggest that dairy intake increases risk of prostate cancer, probably through its calcium content. Reasons for the elevated risk with low-fat milk are unclear, although the reduced content and bioavailability of vitamin D in low-fat milk may play a role. Although 1,25-D has been postulated to reduce risk of prostate cancer and calcium may increase risk by suppressing circulating concentrations of 1,25-D, we failed to see any direct evidence for a protective effect of vitamin D intake in our cohort. Calcium is thought to protect against osteoporosis and colon cancer, and dairy is the primary source of calcium in the US diet. Given the implications of our findings with respect to recommendations to increase both calcium intake and low-fat milk consumption, the mechanisms by which calcium and low-fat milk might increase prostate cancer risk should be clarified and confirmed to verify that calcium is indeed the critical risk factor.

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MT was responsible for analyzing the data and drafting the manuscript. RAB was responsible for identification and confirmation of prostate cancer cases in the dataset and contributed to interpretation of results. BIG contributed to statistical analyses and interpretation of analytic results. RGZ contributed to the original study concept, interpretation of results, and revisions of subsequent drafts of the manuscript, and facilitated acquisition of the dataset for analysis. None of the authors had any conflicts of interest in connection with the research.

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